

1 WHAT IS CLAIMED IS:

2 ~~A pharmaceutical composition comprising a matrix capable of delivering at least one~~
3 ~~therapeutic agent to a bodily compartment under controlled release conditions, said~~
4 ~~matrix comprising a homogeneous mixture of aqueous phase and at least one other phase,~~
5 ~~at least one therapeutic agent present in at least one of said phases, and at least one cross-~~
6 ~~linked polymer physically entrapping said at least one therapeutic agent.~~

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8 2. The pharmaceutical composition of claim 1 wherein said at least one other phase is a
solid phase, an oil phase, or a combination thereof.

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11 3. The pharmaceutical composition of claim 2 wherein said oil phase and said aqueous
12 phase are in the form of an emulsion.

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14 4. The pharmaceutical composition of claim 1 wherein said polymer comprises a backbone
15 selected from the group consisting of a poly(alkylene oxide), carboxymethylcellulose,
16 dextran, modified dextran, polyvinyl alcohol, N-(2-hydroxypropyl)methacrylamide,
17 polyvinyl pyrrolidone, poly-1,3-dioxolane, poly-1,3,6-trioxane, polypropylene oxide, a
18 copolymer of ethylene and maleic anhydride, a polylactide/polyglycolide copolymer, a
19 polyaminoacid, a copolymer of poly(ethylene glycol) and an amino acid, and a
20 polypropylene oxide/ethylene oxide copolymer.

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22 5. The pharmaceutical composition of claim 1 wherein said polymer comprises at least two
23 functional or reactive groups.

1 6. The pharmaceutical composition of claim 5 wherein said functional groups are amino,
2 carboxyl, thiol, hydroxy, or any combination thereof.

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4 7. The pharmaceutical composition of claim 6 wherein said polymer is an poly(alkylene
5 oxide) derivative.

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7 8. The pharmaceutical composition of claim 7 wherein said poly(alkylene oxide) derivative
8 is selected from the group consisting of α,ω -dihydroxy-poly(ethylene glycol) and
 α,ω -diamino-poly(ethylene glycol).

9. The pharmaceutical composition of claim 6 wherein said functional groups are thiol
groups.

10. The pharmaceutical composition of claim 9 wherein said polymer is prepared from
 α,ω -diamino-poly(ethylene glycol) and thiomalic acid; α,ω -dihydroxy-poly(ethylene
glycol) and thiomalic acid; or α,ω -dicarboxy-PEG subunits and lysine, wherein free
carboxy groups on said lysine are derivatized to provide thiol groups.

11. The pharmaceutical composition of claim 9 wherein said thiol groups on said polymer are
cross-linked by thioether or disulfide bonds.

12. The pharmaceutical composition of claim 9 wherein said thiol groups on said polymer are
sterically hindered.

1 13. The pharmaceutical composition of claim 1 wherein said at least one therapeutic agent is
2 selected from the group consisting of a small-molecule drug, a protein, a nucleic acid and
3 a polysaccharide.

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5 14. The pharmaceutical composition of claim 13 wherein said small-molecule drug is
6 selected from the group consisting of an anticancer drug, a cardiovascular drug, an
7 antibiotic, an antifungal, an antiviral drug, an AIDS drug, an HIV-1 protease inhibitor, a
8 reverse transcriptase inhibitor, an antinociceptive drug, a hormone, a vitamin, an
anti-inflammatory drug, an angiogenesis drug, and an anti-angiogenesis drug.

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13 15. The pharmaceutical composition of claim 1 wherein said matrix has at least one
controlled release in-vivo kinetic profile selected from the group consisting of zero order,
pseudo zero order, and first order.

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15 16. The pharmaceutical composition of claim 1 wherein said controlled release conditions is a
16 constant rate of release.

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18 17. The pharmaceutical composition of claim 1 wherein said matrix further comprises an
19 excipient.

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21 18. The pharmaceutical composition of claim 17 wherein said excipient is selected from the
22 group consisting of a monovalent metal ion, a polyvalent metal ion, an anionic polymer, a
23 cationic polymer, a nonionic polymer, a surfactant, and a protein.

1 19. A method for preparing the pharmaceutical composition of claim 1 comprising the steps
of

- 3 i) preparing a mixture comprising at least one therapeutic agent and at least
4 two phases one of which is an aqueous phase, said aqueous phase
5 comprising a polymer having at least two functional groups thereon;
6 ii) cross-linking said polymer under conditions to form a cross-linked matrix
7 having said therapeutic agent entrapped therein.

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11 20. The method of claim 19 wherein said functional groups are thiol groups.

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15 21. The method of claim 20 wherein said conditions that cause cross-linking of said thiol
groups comprises reaction in the presence of an oxidizing agent or reaction with a
cross-linking agent.

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17 22. The method of claim 21 wherein said oxidizing agent is selected from the group
consisting of molecular oxygen, hydrogen peroxide, dimethylsulfoxide, and molecular
iodine.

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19 23. The method of claim 21 wherein said cross-linking agent is a bifunctional disulfide-
forming or thioether-forming cross-linking agent.

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22 24. The method of claim 23 wherein said cross-linking agent is selected from the group
23 consisting of 1,4-di-[3',2'-pyridyldithio(propionamido)butane];

1 α,ω -di-O-pyridyldisulfidyl-poly(ethylene glycol); α,ω -divinylsulfone-poly(ethylene
2 glycol); α,ω -diiodoacetamide-poly(ethylene glycol) and 1,11-bis-maleimidotetraethylene
3 glycol.

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5 25. A method for delivering at least one therapeutic agent to a bodily compartment to an
6 animal under controlled release conditions comprising providing in said bodily
7 compartment a pharmaceutical composition set forth in claim 1.

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9 26. The method of claim 25 wherein said bodily compartment is subcutaneous, oral,
10 intravenous, intraperitoneal, intradermal, subdermal, intratumor, intraocular, intravisceral,
11 intraglandular, intravaginal, intrasinus, intraventricular, intrathecal, intramuscular, and
12 intrarectal.

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14 27. The method of claim 26 wherein said composition is provided to said bodily
15 compartment by a route selected from the group consisting of subcutaneous, oral,
16 intravenous, intraperitoneal, intradermal, subdermal, intratumor, intraocular, intravisceral,
17 intraglandular, intravaginal, intrasinus, intraventricular, intrathecal, intramuscular, and
18 intrarectal.

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20 ~~The method of claim 25 wherein said controlled release conditions occur as a~~
21 ~~consequence of diffusion from said matrix or biodegradation of said matrix by an in-vivo~~
22 ~~degradation pathway selected from the group consisting of reducing agents, reductases,~~

1 ~~A3~~ S-transferases, peptidases, proteases, non-enzymatic hydrolysis, esterases and
2 ~~cat~~ thioesterases

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4 29. The method of claim 25 wherein said providing in said bodily compartment is carried out
5 by forming said matrix immediately prior to or during administration of said matrix to
6 said animal.

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8 30. The method of claim 29 wherein said pharmaceutical composition is capable of being
9 injected as a liquid or semisolid gel through a small gauge needle, begins cross-linking
10 and entrapping said therapeutic agent during injection, and completes cross-linking and
11 physically entrapping said therapeutic agent within several minutes of being injected.

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13 31. The method of claim 25, wherein said controlled release conditions comprise a time
14 course of release of five or more days.

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16 32. The method of claim 31, wherein said time course of release is twenty or more days.

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18 33. The method of claim 25, wherein said releasing comprises a controlled release profile
19 comprising an optional bolus release profile followed by a release profile selected from
20 the group consisting of zero order, pseudo zero order, and first order.

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22 34. A method of administering a controlled release therapeutic agent to a mammal, said
23 method comprising: preparing a solution comprising a hydrogel forming polymer having

1 two or more thiol groups and a plurality of phases, one of which is an aqueous phase, a
2 cross-linking agent comprising two or more thiol-reactive groups, and a therapeutically
3 effective amount of drug; and injecting said mammal with said solution whereby a
4 hydrogel drug depot is formed at the site of injection having said drug temporarily
5 entrapped therein.

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7 35. The method of claim 34, wherein said controlled release therapeutic agent has a kinetic
8 profile comprising an optional initial bolus release profile followed by a release profile
selected from the group consisting of zero order, pseudo zero order, and first order.

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15 36. The method of claim 34 wherein said thiol-reactive cross-linking agent is an oxidizing
agent; 1,4-di-[3',2'-pyridyldithio(propionamido)butane];
 α,ω -di-O-pyridyldisulfidyl-poly(ethylene glycol); α,ω -divinylsulfone-poly(ethylene
glycol); α,ω -diiodoacetamide-poly(ethylene glycol) or 1,11-bis-maleimidotetraethylene
glycol.

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17 ~~A hydrogel composition comprising a homogeneous mixture of aqueous phase and at~~
18 ~~least one other phase, and at least one cross-linked polymer in one of said phases.~~
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